REMARKS

THE WRITTEN DESCRIPTION REJECTION

Claims 1-68 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description. This rejection is respectfully traversed.

The Examiner is of the opinion that the claims contain subject matter not adequately described in the specification. In particular, the Examiner states at page 2 of the Office Action that there is no description in the specification for each m and n greater than 5. The Examiner supports this statement by asserting that the open-ended language of the claims only supports m + n to be 5 and does not support $m + n \geq 5$.

As will be explained below, both the Examiner's reading of the claims and interpretation of the written description requirement is wrong.

As recited in claim 1, the present invention is directed to a method for augmenting soft or hard tissue within a mammalian body, comprising (a) providing a first crosslinkable component having m nucleophilic groups, wherein $m \geq 2$; (b) providing a second crosslinkable component having n electrophilic groups capable of reaction with the m nucleophilic groups to form covalent bonds, wherein $n \geq 2$ and $m + n \geq 5$; (c) applying the first and second crosslinkable components to the tissue; and (d) allowing the first and second crosslinkable components to crosslink *in situ*, wherein the first and second crosslinkable components are biocompatible, synthetic, and nonimmunogenic.

Contrary to the Examiner's assertion, the specification includes several examples to support the numerical limitations recited in the present claims. Directing the Examiner's attention to Examples 1 to 5, there, the reaction of PEGs with multiple nucleophilic groups (*i.e.*, amino groups)and various multifunctionally activated PEGs is shown. The following table summarizes the number of m and n groups per nucleophilic and electrophilic PEG components and the value for the sum of m + n.

Example	**m (# of nucleophilic groups)**	**n (# of electrophilic groups)**	**m + n**
1	2	4	6
2	2	3	5
3	4	4	8
	4	3	7
4	62[1]	4	66
5	4	4	8

As can be seen from the information in the foregoing table, Examples 1-5 clearly disclose chemical reactions between crosslinkable components in which $m + n \geq 5$. Because claims 1-68 are supported by a fully adequate written description, applicants respectfully request withdrawal of this rejection.

THE INDEFINITENESS REJECTION

Claims 22 and 56 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. This rejection is respectfully traversed.

The Examiner requests clarification on how the sulfhydryl electrophilic groups of claims 22 and 56 would form a thioester or a thioether with the sulfhydryl nucleophilic groups.

Claims 22 and 56 recite that the n electrophilic groups of independent claims 1 and 35, respectively, are *sulfhydryl-reactive groups* that form a thioester, thioether, or disulfide *linkage* upon *reaction with the sulfhydryl groups*, the latter of which are recited in claims 21 and 55 as m nucleophilic groups [emphasis added].

The Examiner's rejection indicates that the Examiner appreciates that the two reaction products of claims 22 and 56 can be linked by a disulfide; the Examiner's rejection appears to take issue with only the recited thioester or thioether linkages.

As the language of claim 22 clearly recites that the sulfhydryl nucleophilic groups react with sulfhydryl-reactive electrophilic groups and *not* sulfhydryl electrophilic groups, it follows that the language of claims 22 and 56 is clear and definite.

For purposes of clarification, applicants direct the Examiner's attention to the chemical formulas set forth at paragraphs 0033 to 0037 of the application. To assist the Examiner with the following discussion, applicants emphasize that a sulfhydryl group is represented by the chemical formula -SH; an thioester is represented by the chemical formula R-S-CO-R; and a thioether is represented by the chemical formula R-S-R.

At paragraphs 0033 to 0037 of the specification (page 6), it is explained that the m nucleophilic groups of the present invention may be any of the following representative molecules (represented by "X"): X = $-NH_2$, -SH, -OH, $-PH_2$, $-CO-NH-NH_2$, etc., and can be the same or different; and that the n electrophilic groups of the present invention may be any of the following representative molecules (represented by "Y"): Y = $-CO_2N(COCH_2)_2$, $-CO_2H$, -CHO, $-CHOCH_2$, -N=C=O, $-SO_2CH=CH_2$, $-N(COCH)_2$), -S-S-(C_5H_4N), etc., and can be the same or different.

At paragraph 0034, the reaction of X and Y is shown schematically as follows:

$$\text{polymer - } \mathbf{X}_m + \text{polymer - } \mathbf{Y}_n \rightarrow \text{polymer - } \mathbf{Z} - \text{polymer}$$

Paragraph 0037 explains that Z is a functional group resulting from the union of the nucleophilic group (X) with the electrophilic group (Y).

As is well known in the art, a thioester (represented by the chemical formula R-S-CO-R) may be formed by reaction of a sulfhydryl nucleophilic group (X = -SH) and a sulfhydryl reactive electrophilic group. An example of a sulfhydryl reactive group is provided at paragraph 0036, where $Y = -CO_2N(COCH_2)_2$. The reaction between a crosslinkable component (*e.g.*, a polymer) having a sulfhydryl group and a crosslinkable component having a $-CO_2N(COCH_2)_2$ group to form a thioester linkage is represented as follows:

$$\text{polymer-SH} + \text{polymer-}CO_2N(COCH_2)_2 \rightarrow \text{polymer-S-CO-polymer (Z = thioester)}$$

As noted above, a thioether is represented by the chemical formula R-S-R. Thus, a thioether linkage may be formed, for example, from the reaction between a polymer having a sulfhydryl nucleophilic group (X = -SH) and a sulfhydryl reactive electrophilic group, where $Y = -SO_2CH=CH_2$ as follows (the chemical formula for Y has been written as $(SO_2)CH=CH_2$ to emphasize that SO_2 is sidechain group):

$$\text{polymer-SH} + \text{polymer-}(SO_2)CH=CH_2 \rightarrow \text{polymer-}CH_2(SO_2)\text{-}CH_2\text{-S-polymer (Z = thioether)}$$

Although the foregoing reaction schemes have been presented with polymers having only one electrophilic or nucleophilic group, the reactions can be readily generalized to polymers having multiple nucleophilic ($m \geq 2$) and multiple electrophilic groups ($n \geq 2$).

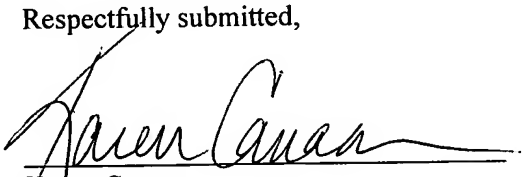
Because the specification clearly describes how to prepare thioether and thioester linkages from crosslinkable components having $m \geq 2$ sulfhydryl groups and $n \geq 2$ sulfhydryl reactive groups, claims 22 and 56 are clear and definite. In view of the foregoing, applicants respectfully request withdrawal of this rejection.

CONCLUSION

With this paper, each of the Examiner's rejections have been fully addressed and overcome. Because there will be no outstanding issues for this matter upon entry of this paper, applicants respectfully request withdrawal of all claim rejections and passage of this application to issue.

Any questions regarding this paper or the application in general may be addressed to the undersigned attorney by telephone at 650.251.7713 or by e-mail at kcanaan@mintz.com.

Respectfully submitted,

By: 

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[1] The number of NH_2 groups was calculated as follows:

$$\frac{\text{Total MW of poly-L-lysine}}{\text{(MW of lysine residue)}} = \text{Total \# of lysines per molecule (1 } NH_2 \text{ group per lysine side chain)}$$

Total # of lysines per molecule = 8000 MW/128 MW = 62 NH_2 groups